general body blood flow are not yet apparent. We have only indirectly demonstrated vasoconstriction in the resting muscle in the arm of disabled cardiac patients during leg exercise. It is highly probable that this occurs in all resting muscle during exercise in such patients, but again further work is needed on this aspect. The vasodilatation in exercising muscle appears to be an irresistible local phenomenon completely dominating any other humoral or neural influences. The maintenance of a normal arterial blood pressure on exercise in these patients with a low and fixed cardiac output, despite the extreme dilatation of the vascular bed in exercising muscle, is essential for the adequate perfusion of brain and heart. It is tolerably certain that vasoconstriction in all resting muscles contributes to this remarkable preservation of the blood pressure during exercise.

The possible dangers of repeated hepatic and renal ischaemia in these patients during exertion have already been discussed. At present we have little knowledge of the oxygen tension levels which will interfere with tissue enzyme and cellular function in these organs. Meanwhile it would appear reasonable to warn such patients not to exercise repeatedly to their maximum tolerance.

Finally, we have not specifically studied the actual mechanisms which are responsible for this highly integrated circulatory economy, and this will be the next stage of the investigation. Such evidence as we have suggests that both humoral and neural mechanisms are involved. It is probable that almost all these changes in regional blood flow in the exercising cardiac patient are also invoked in healthy subjects at higher levels of exertion. Further study of these phenomena in such patients will therefore not only increase our knowledge of heart disease but also strengthen our understanding of the functions of the normal circulation.

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VACCINATION AGAINST WHOOPING-COUGH

THE FINAL REPORT TO THE WHOOPING-COUGH IMMUNIZATION COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND TO THE MEDICAL OFFICERS OF HEALTH FOR BATTERSEA AND WANDSWORTH, BRADFORD, LIVERPOOL, AND NEWCASTLE*

In the previous investigations, reported to the Whooping-Cough Immunization Committee of the Medical Research Council (Medical Research Council, 1951, 1956), there were two main objectives. The first was to obtain, from the results of strictly controlled trials, an assessment of the prophylactic value of pertussis vaccines in children, and the second to determine whether the prophylactic value of vaccines could be assessed by a laboratory test. Field trials were made with a large number of vaccines, and the results showed considerable differences in protective activity, some vaccines giving substantial protection and others hardly any. Laboratory tests also showed that the vaccines differed widely in their ability to protect mice against intracerebral pertussis infection and in their ability to produce specific agglutinin in mice and in children. A comparison between the field and laboratory results showed a substantial degree of correlation between the activity of vaccines in protecting children and their potency in protecting mice. There was also evidence of a correlation between protection in children and the production of agglutinin in both mice and children.

While this work was in progress, Pillemer, Blum, and Lepow (1954) reported the preparation of an antigenic fraction from *Bordetella pertussis*. The preparation involved the sonic disintegration of *B. pertussis* and the treatment of the extract with autoclaved human red cell stromata with the formation of a stromata-antigen complex which contained only a small fraction of the

TABLE I.—*Vaccines and Dosage Schedule*

Vaccine	Date of Preparation	Medium for Growth	Killing Agent and Concentration	Preservative and Concentration	Strains of *B. pertussis*	Other Details of Preparation	No. of Organisms (Millions ml.)	Doses at Monthly Intervals ml.)	Total Dose in Millions of Organisms
V12†	Sept., 1951	BG with human blood	Thiomersalate 0·02%	Thiomersalate 0·013%	293; 324; 360; 357; 358; 332; 343	Michigan method, but with human blood in BG	20,000	1 1 1	60,000
V14	,, 1952	Cohen and Wheeler	,,	,,	,,	Organisms separated from culture fluid	20,000	1 1 1	60,000
V15	,, 1952	,,	Thiomersalate 0·01%	Thiomersalate 0·01%	,,	,, ,, ,,	20,000	1 1 1	60,000
V16	Oct., 1951	BG with human blood	Formalin 0·5% for 24 hours	,,	,,	Same method as for V12 but killed with formalin	20,000	1 1 1	60,000
V17	April, 1953	Cohen and Wheeler	None	,,	134	Method of Pillemer *et al.* (1954)	—	1 1 1	3 ml.
V19	March, 1953	BG with human blood	Thiomersalate 0·02%	Thiomersalate 0·013%	293; 324; 360; 357; 358; 332; 343	Same method as for V12 but containing 25 Lf/ml. of diphtheria F.T.	20,000	1 1 1	60,000 + 75 Lf of F.T.
V20	Same batch as V19, but with no diphtheria F.T.						20,000	1 1 1	60,000

† Used in previous trials (M.R.C., 1956). BG = Bordet–Gengou medium. None of the pertussis vaccines contained an adjuvant.

whole bacillus. This antigenic fraction proved to be highly potent in protecting mice against intracerebral infection, but produced in these animals only a poor agglutinin response (Evans and Perkins, 1955). In view of these observations it was considered important that Pillemer's antigenic fraction should be examined for its protective action in children in order to assess the reliability of the laboratory tests. A field trial was therefore made in which Pillemer's antigenic fraction was compared with a whole bacterial vaccine.

Two further studies were also included in this new series of trials. In one, a comparison was made of two vaccines grown in fluid medium with a vaccine grown on solid medium, using the same strains of *B. pertussis* in all three vaccines. In the other, a comparison was made between a pertussis vaccine alone and the same pertussis vaccine mixed with diphtheria toxoid (F.T.) containing 25 Lf/ml.

Details of the seven vaccines used are given in Table I; all of them except Pillemer's antigen were prepared in this country.

Field Trials

The plan of the trials was described in detail in the previous reports (Medical Research Council, 1951, 1956). All children were given one of the pertussis vaccines under test, and in each trial two or three vaccines were contrasted. Each vaccine was designated by a code letter and number. Three injections were given at monthly intervals, and the vaccinated children were subsequently visited by nurse-investigators at monthly intervals for between two and three years after the third injection. The visitors had no record of the vaccine which a particular child had received.

Similarity of Groups in all Trials

The similarity of the groups of children in each trial was tested as described in previous reports. In each trial the characteristics of the groups were similar with respect to their ages, the number of household contacts, and the incidence of infectious diseases other than pertussis (Table II). The differences observed in the number of other infectious diseases in Bradford can probably be accounted for by the small number of children in this area (see Table III). The larger size of family in Bradford resulted from the deliberate selection of families for follow-up as described in the next section.

TABLE II.—*Similarity of Groups*

Area	Vaccine	Average Age (Mths)	No. of Other Children/ Household under 15 Years of Age	Average No. of Infectious Diseases (Other than Pertussis)/ Child during the Follow-up
Newcastle	V14 (liquid medium)	18	0·75	0·20
	V12 (solid medium)	18	0·70	0·22
	V15 (liquid medium)	16	0·77	0·20
Bradford	V14 (liquid medium)	20	1·87	0·39
	V12 (solid medium)	19	1·77	0·48
	V15 (liquid medium)	19	1·74	0·61
Liverpool	V17 (Pillemer's antigen)	14	0·89	0·27
	V16 (whole bacteria)	14	0·86	0·27
Battersea and Wandsworth	V19 (mixed)	10	0·72	0·26
	V20 (plain)	9	0·73	0·27

Trials with Vaccines made in Liquid Medium, V14 and V15, and on Solid Medium, V12

Trials were made with vaccines V14, V15, and V12 in two areas, Newcastle and Bradford. Vaccines V14 and V15 were grown in liquid medium and vaccine V12 was grown on solid medium (Table I). The trials were begun in 1953 and completed in October, 1956. Most

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Laboratory diagnostic tests were made by: Dr. A. J. H. Tomlinson (Battersea and Wandsworth), Dr. H. G. M. Smith (Bradford), Professor D. T. Robinson (Liverpool), Dr. A. I. Messer (Newcastle).

Laboratory tests for antigenic potency were made by: Mr. A. F. B. Standfast (Lister Institute); Dr. Margaret Pittman (U.S. National Institutes of Health, Bethesda); the Glaxo Laboratories Ltd.; the Lederle Laboratories, Pearl River, New York; Dr. Naomi Datta (Central Public Health Laboratory, Colindale); Dr. D. G. Evans and Dr. F. T. Perkins (Medical Research Council Laboratories, Hampstead).

The field trials were put in train and supervised by Dr. W. C. Cockburn.

The analysis of the field and laboratory results were made and the report prepared by Dr. P. Armitage, Dr. W. C. Cockburn, Dr. D. G. Evans, Dr. J. O. Irwin, Dr. J. Knowelden, and Mr. A. F. B. Standfast.

of the children were vaccinated in local authority clinics, but in Newcastle vaccine was also issued to general practitioners. In the clinics, children born in the first ten days of any month were given vaccine V14 (liquid medium), children born in the second ten days vaccine V12 (solid medium), and children born in the remainder of the month, vaccine V15 (liquid medium). As this method of allocation to vaccine groups was inconvenient for general practitioners, a list of all practitioners in Newcastle was obtained and the names were randomly placed in three groups of approximately equal size. Vaccine V14 was allocated for issue to one of these groups, vaccine V12 to the second, and vaccine V15 to the third. Each practitioner therefore received the same vaccine—that allocated to the group to which he belonged—during the whole course of the trial, so that in any one practice all the children were given the same vaccine. Although the method of allocation in the clinics in Newcastle gave an even distribution with just over 600 children receiving each vaccine, the distribution through general practitioners was less successful, about 400 children receiving V14 (liquid medium), about 800 V12 (solid medium), and about 600 V15 liquid medium).

Children from 4 months to 4 years of age were included in the study. Consent for inoculation was received from the parents of 3,990 Newcastle children; 3,688 of these children (92%) completed the course of injections. In the Bradford trial a vaccinated child was followed up only when it came from a family in which there was at least one other unvaccinated child with no history of pertussis. There were 258 such children out of a total of about 3,000 vaccinated.

Incidence of Pertussis.—The number of exposures and cases in the two trials was small. *B. pertussis* was isolated from 6 of the 7 cases in the Bradford trial and from 7 of the 32 in the Newcastle trial. It is clear from Table III that the attack rate per 1,000 child-months was highest in children given vaccine V14 (liquid medium) and lowest in children given vaccine V15 (liquid medium). In Table IV are shown the attack rates after "Home" and "Other" exposures, and the number of cases with no history of exposure. By these methods of assessment also, V14 (liquid medium) provided less protection than V12 (solid medium), and V12 less protection than V15 (liquid medium).

The three vaccines were consistently placed in the same order in Newcastle and in Bradford both by the attack rate per 1,000 child-months and by the home exposure attack rate; the two areas were therefore combined in Tables III and IV. Not all the differences were formally significant; by the attack rate per 1,000 child-months, V14 (liquid medium) was significantly worse than either V12 (solid medium) or V15 (liquid medium) ($P<0.01$), but the difference between V12 and V15 was not significant at the 5% level. The differences in the home exposure attack rates between V14 and V12 and between V12 and V15 were not significant, although V14 was significantly worse than V15 ($P<0.01$).

These differences in the performance of the three vaccines were not the result of the uneven allocation through general practitioners. The data were analysed separately and showed that both for the children allocated through clinics and for those through general practitioners the same order emerged, with the lowest rates for V15 and the highest for V14.

Whether significant or not, the differences between the protection afforded by the three vaccines cannot be interpreted in relation to the type of medium used, since the two liquid-medium vaccines, V14 and V15, occupied the extreme positions, with the solid-medium vaccine, V12, lying intermediate in performance.

TABLE III.—*Number of Cases of Pertussis and Attack Rates Per 1,000 Child-Months of Observation*

Area	Vaccine	No. Followed Up	Total Duration of Observation (Child-months)	Cases of Pertussis	Attack Rate/1,000 Child-months
Newcastle	V14 (liquid medium) ..	1,015	18,809	19	1·01
	V12 (solid ,,) ..	1,432	27,624	10	0·36
	V15 (liquid ,,) ..	1,241	24,411	3	0·12
Bradford	V14 (liquid ,,) ..	87	1,976	4	2·02
	V12 (solid ,,) ..	81	1,888	2	1·06
	V15 (liquid ,,) ..	90	2,005	1	0·50
Newcastle and Bradford combined	V14 (liquid ,,) ..	1,102	20,785	23	1·11
	V12 (solid ,,) ..	1,513	29,512	12	0·41
	V15 (liquid ,,) ..	1,331	26,416	4	0·15
Liverpool	V17 (Pillemer's antigen)	2,179	49,680	9	0·18
	V16 (whole bacteria) ..	2,260	51,326	23	0·45
Battersea and Wandsworth	V19 (mixed)	2,490	47,046	15	0·32
	V20 (plain)	2,154	41,678	10	0·24
	Totals	13,029	266,443	96	0·36

Trial with Pillemer's Antigenic Fraction, V17, and Whole Bacterial Vaccine, V16

The trial of Pillemer's antigenic fraction was made in Liverpool in children 4 months to 4 years of age. Some of them were vaccinated in clinics and some by general practitioners. In clinics, children born on odd days of the year were given Pillemer's antigen V17 and those born on even days were given the whole bacterial vaccine V16. General practitioners in Liverpool were divided, by random sampling, into two

TABLE IV.—*Number of Cases of Pertussis and Percentage Attack Rates by Type of Exposure*

Area	Vaccine	No. of Exposures		Cases of Pertussis			Attack Rates %	
		Home	Other	After Home Exposure	After Other Exposure	Without Known Exposure	Home Exposure	Other Exposure
Newcastle	V14 (liquid medium)	19	30	10	4	5	53	13
	V12 (solid ,,)	16	61	4	3	3	25	5
	V15 (liquid ,,)	16	45	1	2	0	6	4
Bradford	V14 (liquid ,,)	8	2	3	0	1	38	0
	V12 (solid ,,)	9	0	2	0	0	22	0
	V15 (liquid ,,)	7	0	1	0	0	14	0
Newcastle and Bradford combined	V14 (liquid ,,)	27	32	13	4	6	48	13
	V12 (solid ,,)	25	61	6	3	3	24	5
	V15 (liquid ,,)	23	45	2	2	0	9	4
Liverpool	V17 (Pillemer's antigen)	38	100	3	0	6	8	0
	V16 (whole bacteria)	45	101	7	5	11	16	5
Battersea and Wandsworth	V19 (mixed)	40	49	4	5	6	10	10
	V20 (plain)	44	34	5	2	3	11	6
	Totals	242	422	40	21	35	17	5

equal groups. One group was issued with V17 and the other with V16 during the period of the trial. As in the Newcastle and Bradford trials, therefore, all the children in a particular general practice received the same vaccine. Altogether the parents of 5,216 children agreed to take part in the study and 4,439 of the children (85%) completed the course of injections; 2,179 received vaccine V17 and 2,260 vaccine V16.

Local and General Reactions.—As Pillemer's antigen had not been used on a large scale previously, a special study was made of reactions. The first 501 children given injections in the trial were visited 48 to 72 hours after each of their injections and the degree of local and general reactions was recorded. Thirty of the children had one injection only and 14 had two injections only, so that the number visited after the second injection was 471, and after the third injection 457. As can be seen in Table V, more children had reactions

TABLE V.—*Liverpool Trial. Percentage of Children with Local and General Reactions After Receiving Pillemer's Antigen V17 and Whole Bacterial Vaccine V16*

	First Injection		Second Injection		Third Injection	
	V17 (261)	V16 (240)	V17 (243)	V16 (228)	V17 (232)	V16 (225)
Children without local or general reactions ..	27	46	20	33	17	25
Children with local reactions only	19	17	12	15	18	22
Children with general reactions only	21	23	28	25	24	23
Children with both local and general reactions ..	33	14	40	27	41	30
All children with reactions ..	73	54	80	67	83	75

Figures in parentheses are the number of children visited.

after Pillemer's antigen V17 than after the whole bacterial vaccine V16. Not only were there more children with reactions, but the reactions were more severe. For example, of children with a local reaction (redness, with or without swelling), the percentage with reactions 1 in. (2.5 cm.) in diameter or greater was, in the V17 group, 76 after the first injection, 79 after the second, and 78 after the third. In the V16 group the corresponding percentages were 57, 61, and 66. The mothers of six children on V17 but none of the mothers of children on V16 gave the severity of the reaction as the reason for not having the course completed.

The higher incidence of reactions from Pillemer's antigenic fraction may have been due to the higher concentration of the antigen. In preparing the suspension of the antigen for use in the field, the dilution factor employed was based on the results of mouse-protection tests, and, though it was considered from these tests that a less concentrated antigen than the one chosen might give good protection in children, the higher concentration was used so as to obtain more conclusive results.

Incidence of Pertussis.—Though the numbers of cases and exposures were small, the results by the different methods of assessment showed that there were fewer attacks in children given Pillemer's antigen V17 than in children given the whole bacterial vaccine V16 (Tables III and IV). The difference in the attack rates per 1,000 child-months reached the 5% level of significance; the difference in attack rates after the different types of exposure was not significant. Of the 32 cases, five were confirmed bacteriologically.

Trial with Mixed Diphtheria-Pertussis Vaccine, V19, and Plain Pertussis Vaccine, V20

Mixed diphtheria–pertussis vaccine, V19, was compared with plain pertussis vaccine, V20, in Battersea and Wandsworth in children 4 months to 4 years of age. As most children are immunized against diphtheria at about 1 year of age, nearly all children in the trial were between 4 and 18 months old. The children were injected in the local authority clinics. Those born on even days of the year were given plain pertussis vaccine, V20, and those born on odd days were given the mixed vaccine, V19, the pertussis component of which was from the same batch as the plain vaccine. Children given the plain vaccine were later immunized against diphtheria with two doses of A.P.T. All children given three injections of pertussis vaccine alone or in the mixture were taken into the follow-up group, the first visit to the home being made one month after the third injection; those given the plain vaccine had not at this time necessarily received their injections of diphtheria toxoid. The parents of 5,738 children agreed to have them inoculated and 5,260 children (92%) completed the course of injections. Vaccination was temporarily suspended when the incidence of poliomyelitis was high, and 616 of the children had intervals of more than six weeks between successive injections. These children were omitted from the trial, leaving 4,644 under observation. Of these, 2,490 were given the mixed vaccine, V19, and 2,154 the plain vaccine, V20.

Local and General Reactions.—These were recorded in over 250 children visited the day after each injection. The reactions were similar in incidence and severity to those seen in the previous pertussis vaccine trials (Medical Research Council, 1951, 1956) and no consistent differences were seen between children given the mixed vaccine and children given the plain pertussis vaccine.

Incidence of Pertussis.—From the small number of exposures and cases observed during the study (Tables III and IV) there was no evidence of a difference in protective properties between the mixed and plain vaccines. Bacteriological proof was obtained from 3 of the 25 cases.

Serological Tests.—In groups of children the diphtheria antitoxin levels induced by the mixed vaccine, V19, were compared with those induced by diphtheria P.T.A.P. The P.T.A.P. used had a strength of 50 Lf/ml. and was given in two doses, each of 0.5 ml., at an interval of one month. Four separate groups of children were included in this comparison, two groups receiving mixed vaccine and two diphtheria P.T.A.P. Serum was taken from one of the groups on each vaccine at one to two months after the last injection

TABLE VI.—*Results of Serological Tests in the Mixed Vaccine Trial*

Vaccine	No. of Children	Average Age (Mths)	Months after Last Injection when Serum Taken	No. of Children with Diphtheria Antitoxin Units/ml. of:				
				<0·001	0·001–0·01	0·01–0·1	0·1–1	1–10
V19 mixed vaccine	64	8 5	1–2	1	1	5	45	12
	37	9·2	6	0	0	8	23	6
	Both groups 101	8·8	—	1	1	13	68	18
Diphtheria P.T.A.P.	27	10·3	1–2	0	0	0	4	23
	22	12·0	6	0	0	0	12	10
	Both groups 49	11·1	—	0	0	0	16	33

and from the other two groups at six months. The average age of the children who received P.T.A.P. was slightly higher than that of the children receiving the mixed vaccine (Table VI). The results show that a slightly better diphtheria antitoxin response was induced by two doses of the P.T.A.P. than by three doses of the mixed vaccine.

Convulsions and Poliomyelitis in All Trials

Information on the occurrence of convulsions was obtained by the same means as in the previously reported trials (Medical Research Council, 1956). In all the trials here reported about 16,000 children were given three injections (including those inoculated but not followed up in Bradford). Fifteen of them had convulsions within 28 days after injection. Six of the children had convulsions within 72 hours after injection, the period in which Byers and Moll (1948) have suggested that vaccine-precipitated convulsions usually become manifest. The remaining nine children had convulsions 4 to 28 days after injection. One of the six children with convulsions within 72 hours after injection had a second convulsion 12 months after the first. Three of the nine children whose first convulsion occurred 4 to 28 days after injection had recurrent convulsions; two each had one recurrence 6 and 8 months after the first, and one had two recurrences 4 and 12 months after the first. There was therefore no indication that children who had their first convulsion less than 72 hours after inoculation were more likely to have repeated convulsions than children whose first convulsion occurred more than 72 hours after injection.

Paralytic poliomyelitis was diagnosed in eight children over the course of the studies, in which some 48,000 injections were given. Four of the cases were in Liverpool—two in Battersea and Wandsworth, and two in Newcastle. Only two cases (both in Newcastle) were in children injected less than 28 days before onset of symptoms. They were children in the same residential nursery; both had facial paralysis but no other paralysis and both recovered completely.

Agglutinin Production Tests

Five of the vaccines—V12, V14, V15, V16, and V17—were tested for their ability to produce agglutinin in mice, using the method of Evans and Perkins, who have already published the detailed results (Evans and Perkins, 1953, 1954, 1955). Table VII gives the agglutinin responses obtained with each vaccine to a total dose of 0.5 ml., which, for the whole bacterial vaccines, was equivalent to 10×10^9 organisms. Table VII also includes the agglutinin responses and the home exposure attack rates for the vaccines reported previously (Medical Research Council, 1956). It is evident that with the whole bacterial vaccines there is a general correlation between protection in the field and agglutinin response in mice, vaccines showing good protection giving good agglutinin response and those showing poor protection giving poor agglutinin response. However, with Pillemer's antigenic fraction, V17, which showed good protection in children, only a relatively poor agglutinin response was obtained in mice. It is therefore clear that agglutinin production in mice cannot always be taken as evidence of protective activity in children.

A similar conclusion was reached from the results of agglutinin production tests made in children by Dr. Naomi Datta. Each of the seven vaccines used in these final trials was tested in groups containing between 30 and 70 children, aged 9 to 17 months, and serum was taken one to two months after the third injection. The results are given in Table VII together with those from the previous report (Medical Research Council, 1956). It is evident that the degree of protection afforded by the vaccines was not always related to their ability to produce agglutinin in children. Pillemer's antigen, V17, although giving good protection, produced an agglutinin response which was less than those produced by whole bacterial vaccines with equally good protective properties.

TABLE VII.—*Comparison Between Results of Field Trials and Laboratory Tests*

Vaccine	Field Trials		Laboratory Tests			
	Home Exposures		Mean Agglutinin Titre		Potency by Mouse-protection Test in Terms of Vaccine G61	
	Cases/ Exposures	Attack Rate (%)	In Mice	In Children	Log Ratio	Ratio
V11	2/52	4	1,259	291	1·023	10·55
D231	3/41	7	1,125	NT	0·594	3·93
*V17	3/38	8	63	112	0·983	9·62
*V15	2/23	9	1,800	389	1·090	12·30
V12	9/104	9	1,990	279	0·928	8·47
*V19	4/40	10	NT	362	1·157	14·35
*V20	5/44	11	,,	256	1·183	15·24
V9	17/132	13	2,820	NT	0·958	9·08
V8	59/428	14	708	211	0·851	7·10
*V16	7/45	16	5,000	84	0·899	7·93
087860	8/36	22	NT	NT	0·300	2·00
*V12	6/25	24	1,990	141	0·857	7·19
V10	25/85	29	644	200	0·582	3·82
G61 (ref)	7/23	30	NT	NT	0	1·00
G174	14/47	30	,,	,,	−0·944	0·11
*V14	13/27	48	2,716	135	0·898	7·91
V3b	35/65	54	NT	6	−0·045	0·90
V7	9/16	56	16	5	0·012	1·03
V6	12/21	57	49	5	−0·095	0·80
V3	66/109	61	13	4	−0·335	0·46
V5	11/18	61	14	4	−0·475	0·34
V5a	31/51	61	NT	12	−0·159	0·69
V4	53/72	74	17	7	0·030	1·07
V1	73/93	78	15	4	−0·829	0·15
V2	89/102	87	10	4	−1·504	0·03

* Vaccines used in the final series of field trials. NT = not tested.

Mouse-protection Tests

The vaccines used in the present field trials were compared by the intracerebral mouse-protection test, both against each other and against some of the vaccines discussed in the 1956 report, particularly vaccine V8, which was previously used as a reference vaccine. The method of assay followed the same plan as in the previous investigation (Medical Research Council, 1956). From assays conducted by Mr. A. F. B. Standfast, Dr. Margaret Pittman, and the Lederle Laboratories, a combined estimate was made of the relative potency of each vaccine in terms of V8, and hence, by using Table IX of the last report, in terms of vaccine G61, since all vaccines used in the previous studies had been compared with G61. The results are shown in Table VII, which also includes those from Table IX of the previous report. In general the figures shown are the logarithms of the relative potencies of equal doses, expressed as numbers of organisms. However, in the case of Pillemer's antigenic fraction, V17, the dose of which cannot be expressed as numbers of organisms, the potency of 1 ml. was compared with that of $20,000 \times 10^6$ organisms of G61, since vaccine V16, with which Pillemer's antigen had been compared in the field, had a concentration of $20,000 \times 10^6$ organisms per ml.

In the comparison between field and laboratory results which was presented in the 1956 report, a correction was made for possible deterioration of the vaccines. Further examination of the ImD_{50} values (doses providing 50% of protection among mice) suggests that over long periods of time these do not follow a steady trend, and that their long-term changes may well be

caused by fluctuations in test conditions rather than deterioration of the vaccines. We therefore follow Kendrick, Eldering, Hornbeck, and Baker (1955), Armitage and Perry (1957), and Ungar and Basil (1957) in assuming no deterioration.

If consideration is restricted first to vaccines compared in the field at the same time and in the same place, the only significant difference between home-exposure attack rates is provided by the Newcastle trial, in which V14 was associated with a significantly higher attack rate than V15, V12 occupying a middle position. In the laboratory tests V14 and V12 were significantly less potent than V15. There is thus a little confirmatory evidence, and no contradiction, between the two types of data.

Table VII also shows the home-exposure attack rate for each vaccine, and in the Chart these attack rates are plotted against the logarithm of the potency ratios in terms of G61, uncorrected for deterioration. The absence of a correction for deterioration hardly affects the relationship between field and laboratory results, as may be seen by comparing the present chart with that in the 1956 report. The results for the new vaccines confirm the general relationship in that as a group they show low home-exposure attack rates and high potencies. The home-exposure attack rate for V14 is higher than might have been expected from a knowledge of its potency, but it must be remembered that both the log-potency ratio and the home-exposure attack rates are subject to appreciable sampling errors.

The British Standard vaccine has been estimated by Armitage and Perry (1957) to have a log-potency ratio of −0.173 in terms of the vaccine V12, from which it was prepared. Since the log-potency ratio of V12 in terms of G61 is estimated to be 0.928, that of the British Standard in terms of G61 is 0.928−0.173=0.755. This value is indicated on the horizontal axis of the chart by an arrow.

Summary

The results are given of field trials involving seven different vaccines, in which a total of 13,029 children were followed up for two to three years. It was shown that one of two pertussis vaccines prepared in liquid medium was not significantly different in its protective properties from one prepared on solid medium; the other was significantly different, but the reason for this was not clear and the number of observations was small. It was also shown that the protective antigen extracted from *B. pertussis* by Pillemer *et al.* (1954) was, in the concentration used, more effective in its protective action than a whole bacterial vaccine, but caused more reactions. It was further shown that the protective action induced by a pertussis vaccine mixed with diphtheria toxoid (F.T.) was similar to that induced by the same pertussis vaccine alone.

The results of serological tests in the mixed vaccine trial showed that the diphtheria antitoxin response was slightly less in a group of children receiving 3 doses of the mixed vaccine than in a similar but slightly older group who received 2 doses of diphtheria P.T.A.P.

Serological tests were also made of the ability of the pertussis vaccines to produce specific agglutinin in mice and in children. The results, together with those previously obtained, were compared with the degree of protection afforded in children. A general correlation was obtained with whole bacterial vaccines between protection and agglutinin production, but not with Pillemer's antigenic fraction. Thus, agglutinin production cannot always be taken as evidence of protective activity.

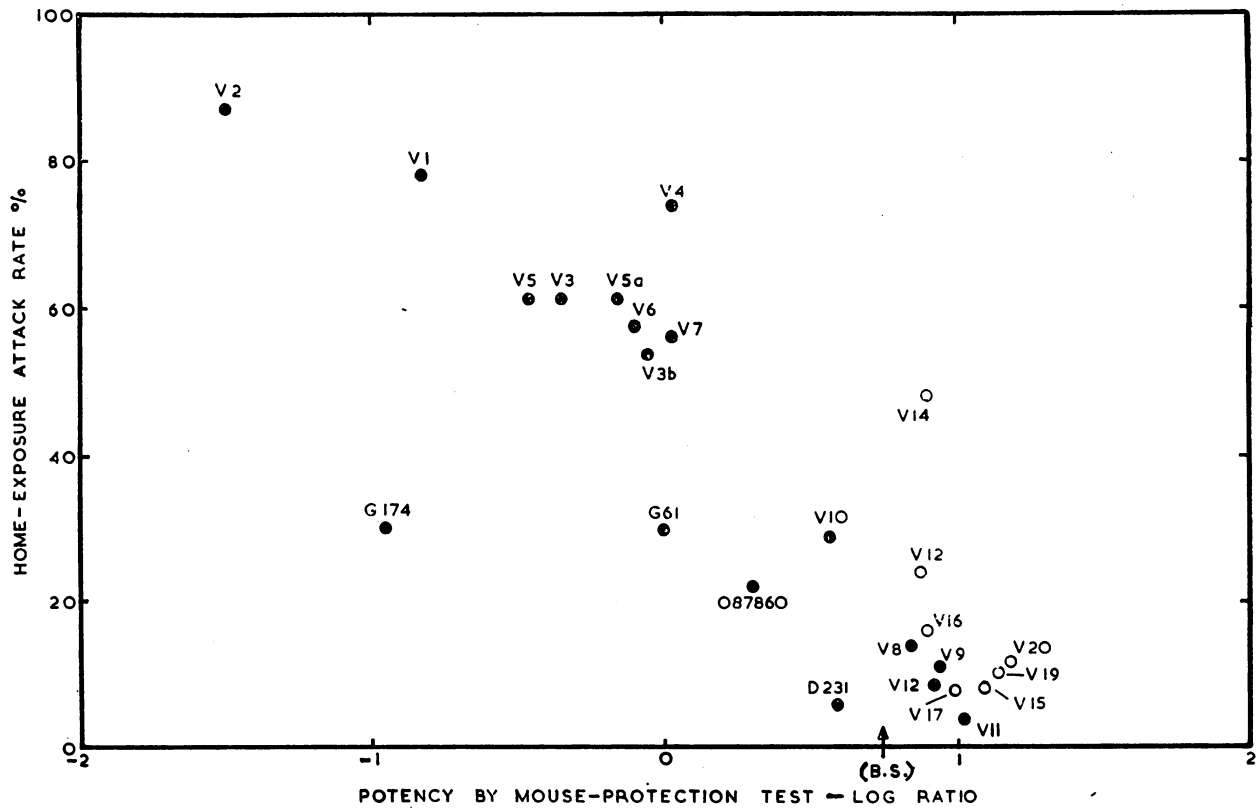

Chart showing the relationship, with 25 pertussis vaccines, between home-exposure attack rate in the field and potency as estimated by the mouse-protection test. Black circles=Vaccines described in the 1956 report. Open circles=Vaccines described in the present report. The log potency of the British Standard Vaccine is shown by an arrow.

The seven vaccines were assayed for their protective potency by the intracerebral mouse-protection test and their relative potencies compared together with those of the 18 vaccines used in the previous studies. A comparison between the field and laboratory results of all 25 vaccines showed a high degree of correlation between the potency of the vaccines in protecting mice against intracerebral infection and their ability to protect children against pertussis.

These findings confirm the previous observations and strengthen the conclusion that only those pertussis vaccines which have been shown, by the intracerebral mouse-protection test, to have an adequate potency in relation to the British Standard Pertussis Vaccine should be used in whooping-cough prophylaxis.

GENERAL CONCLUSIONS

The series of investigations made by the Whooping-Cough Immunization Committee of the Medical Research Council, which have now been completed, were begun in 1942. They were designed to assess the value of pertussis vaccines in protecting children against whooping-cough and to determine whether the prophylactic value of vaccines could be assessed by a laboratory test. In the first studies, made from 1942 to 1944, controlled trials were carried out in Oxford City with children attending welfare clinics and day nurseries, and also in Oxfordshire, Berkshire, and Buckinghamshire with children in residential nurseries. The results of these trials showed that there was no significant difference in the incidence or severity of the disease between the vaccinated and unvaccinated groups (McFarlan, Topley, and Fisher, 1945).

These unfavourable results were not in keeping with some of those reported in America, and it was therefore decided to organize further field trials with a number of pertussis vaccines prepared by different laboratories and to include vaccines of both British and American origin. Three series of controlled trials were made, from 1946 to 1950 in Edmonton, Leeds, Manchester, Tottenham, Wembley, and West Ham; from 1948 to 1951 in Cardiff, Leyton, Manchester, Oxford, Poole, and Walthamstow; and from 1951 to 1954 in Cardiff, Leeds, Manchester, Oxford, Poole, Tottenham, and Wembley (Medical Research Council, 1951, 1956). In all, 19 vaccines were used and more than 36,000 children attending local authority clinics were inoculated and followed up for two to three years. The results of the trials clearly showed that it was possible by vaccination to produce a high degree of protection against the disease, as shown by the substantial reduction in the attack rate amongst home contacts, and, in those cases where vaccination failed to give complete protection, to reduce the severity and duration of the disease. The results also showed that the different vaccines employed varied a great deal in their protective action; the poorest gave an attack rate in home contacts of 87%, and the most effective an attack rate of 4%.

At the same time as the field trials were in progress laboratory tests were made, in both Britain and America, in which the vaccines were extensively tested for their ability to protect mice against intracerebral pertussis infection (World Health Organization, 1953), and also for their ability to produce agglutinin in mice (Evans and Perkins, 1953, 1954). Some of the vaccines were also tested for their ability to produce agglutinin in children. A comparison between the field and laboratory results showed a correlation between protection in children and the three laboratory tests: (*a*) protection in mice, (*b*) production of agglutinin in mice, and (*c*) production of agglutinin in children.

Although the three laboratory tests gave results parallel with those obtained in the field, it was recognized that there still remained the important question of which test was the most direct measure of the factor or factors responsible for inducing immunity in children. An opportunity to investigate this problem was given by the work of the late Professor Louis Pillemer and his colleagues (1954), who had prepared from *B. pertussis* an antigenic fraction which protected mice against intracerebral pertussis infection, but which produced a poor agglutinin response in mice (Evans and Perkins, 1955). This antigenic fraction was included in the final series of field trials, which were made from 1953 to 1957. In this series seven vaccines were used and more than 13,000 children in Battersea and Wandsworth, Bradford, Liverpool, and Newcastle were inoculated in local authority clinics and by general practitioners and followed up for two to three years (present report).

The results of the trial with Pillemer's antigenic fraction, in which there were about 4,500 children, showed that it was able to induce a high degree of immunity in children. It was also shown that the fraction produced an agglutinin response less than that produced by whole bacterial vaccines with equally good protective properties. It was therefore clear that although agglutinin production in mice and children may sometimes, especially with whole bacterial vaccines, parallel protective activity in children, the results of the field and laboratory tests with Pillemer's antigen indicated that this relation may not always hold good. It was therefore considered that the mouse protection test was the most satisfactory in assessing prophylactic activity. This test is correlated with protection in children, and in mice it measures protection from infection with a virulent strain of *B. pertussis*.

A British Standard Pertussis Vaccine has been prepared from one of the batches of vaccine giving good protection in the field trials, and by employing this standard in comparative mouse-protection tests it will now be possible to ensure that vaccines which are used for immunization against whooping-cough will produce substantial protection against the disease.

The Whooping-Cough Immunization Committee of the Medical Research Council and the medical officers of health in the areas where the trials were made are grateful to the parents who consented to have their children inoculated. They also wish to thank the Glaxo Laboratories Ltd., the Lister Institute of Preventive Medicine, and the Lederle Laboratories, Pearl River, for the free supply of the pertussis vaccines. They are particularly indebted to the late Professor Louis Pillemer, of the North Western Reserve University, Cleveland, Ohio, who prepared the protective antigen for the Liverpool trial and who gave much help and advice during visits to this country and by correspondence.

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